REMARKS

For ease of prosecution, previously pending Claim 71 has been essentially split into two claim sets, Claims 71, 73, 75 and 77 (one group) and Claims 79-82 (second group). Claims 72, 74, 76 and 78 have been cancelled herein.

Support for polypeptides comprising HD1 (amino acids 177-204 of SEQ ID NO:15) or HD2 (amino acids 349-383 of SEQ ID NO:15), but not both, can be found, *inter alia*, in original Claims 21 to 29, especially in original Claim 28 of the present application.

Claim 28 refers to a peptide comprising the HD1 or HD2 of Figure 7. Claim 28 depends on Claim 26 which mentions that said peptide's partner proteins are Dol1 and β-Catenin (β-Cat). Claim 28 also depends on Claim 25 which refers to compounds interfering with the binding to domains comprising at least one HD common to hLgs or dLgs (Claims 23 and 24) for inhibiting the interaction between partner proteins to these domains. In short, these claims are directed to polypeptides comprising HD1 or HD2 which bind to Dol1 and β-Cat, respectively, for inhibiting the interaction between Dol1 and β-Cat to Lgs.

Claim 29 relates to the use of a peptide of Claim 28 comprising HD1 or HD2 in a pharmaceutical composition.

Figures 12 and 13 (see also pages 16-18 of the present specification), demonstrate the binding of HD2 to β-Cat and that mutations in HD2 abolish binding of Lgs to β-Cat.

Figures 15A and 15B demonstrate the inhibitory effect of Lgs HD2 peptides on tcf-driven luciferase activity in carcinoma cells with a constitutively active Wnt pathway, in comparison to

the stimulatory activity of the complete hLgs comprising both domains (the sequence described by Tang et al). The inhibitory action of a Lgs peptide with only one of said HDs is clearly demonstrated in the present specification.

On page 23, last paragraph to page 24, second paragraph, the interaction of Lgs with β-Cat by HD2 and with Dol1 by HD1 is also clearly taught.

Lgs or peptides thereof comprising both HDs are positive regulators of the Wg/Wnt pathway (see page 24, second paragraph and Figure 6 of the present specification), while those peptides of the invention that comprise only one of HD1 or HD2 and bind to Dol1 or β-Cat, respectively, are negative (i.e., inhibitory) regulators of the same pathway. Page 26, lines 1-5, also states that Lgs peptides comprising at least one HD can be used for blocking Lgs function in cancer cells. In tumor cells peptides will bind to their interacting partner, e.g., β-Cat if HD2 peptide is chosen. Dol1 binds specifically to HD1 (amino acids 177-205) of Lgs (page 37, first paragraph).

Furthermore, support for the amended claims can be found in Example XIII on page 44 (middle of the page), wherein it is stated that small peptides including HD1 or HD2 strongly inhibit tcf-driven luciferase activity in carcinoma cells.

Hence, the amendments to the claims and new Claims 79-82 do not constitute new matter, and thus entry is requested.

On page 2 of the Office Action, the Examiner rejects Claims 71-78 under 35 U.S.C. § 112, first paragraph as lacking written description.

Specifically, the Examiner states that the specification only provides written description for polypeptides "consisting of" residues 177-204, 349-383 and 199-392. It is the Examiner's position that these species are not representative of the claimed genus of polypeptides "comprising" the claimed sequence because the genus is highly variant, the specification does not provide a description of which polypeptides within the genus have the function claimed and there is no reliable correlation between the structure provided (the sequence of peptide fragments) and the claimed function (inhibits tcf-driven luciferase activity in colon cancer cells).

On page 2 of the Office Action, the Examiner notes Applicants' argument that it is homology regions HD1 and HD2 which act to inhibit tcf-driven luciferase activity in colon cancer cells, and the remaining sequences which may be present are not critical. However, the Examiner contends that this argument is not persuasive because Applicants argue in response to the prior art rejection (see below) that additional sequence can actually eliminate the claimed function.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

The claims have been amended to make clear that the claimed polypeptides do not contain both the HD1 and HD2 domains at the same time, and further new Claims 79-82 require that the polypeptides bind to Doll or β-cat.

Applicants respectfully submit that that the Examiner's rejection should be withdrawn in view of these amendments and the abundant support in the specification for peptides

comprising either HD1 or HD2 for binding Lgs partner proteins Dol1 and β-Cat as negative regulators of the Wnt pathway by inhibiting tcf-driven luciferase activity in colon cancer cells. Applicants have demonstrated a reliable correlation between the structure provided (the sequence of peptide fragments comprising HD1 or HD2) and the claimed function (inhibits tcf-driven luciferase activity in colon cancer cells) in the present specification. Figures 15A and 15B clearly distinguish the peptides of the invention (HD1 or HD2) from those of the prior art (hLgs) by their function.

The Examiner notes Applicants' argument that the peptide of amino acids 189-393 inherently inhibits luciferase activity in colon cancer cells, which the Examiner contends contradicts Applicants' arguments that the polypeptide of Tang et al, which comprises amino acids 189-393, would not have this activity, and the evidence that the Roose et al polypeptide does not have such activity.

The Examiner is requested to note that the reference in the specification, at page 44, to peptides hLgs (199-392) or hLgs (279-392) in the context of peptides including HD1 is an obvious error because the HD1 resides in amino acids 177 to 204 of hLgs which are absent for the most part or absent completely in these particular peptides. In this context, the last sentence on said page 44 also indicates that the above peptides can be used for therapy of Wnt pathway overactivated diseases.

Accordingly, Applicants respectfully submit that the claims do have written description in the specification, and thus request withdrawal of the Examiner's rejection.

On page 7 of the Office Action, the Examiner rejects Claims 71-78 under 35 U.S.C. § 102(e) as being anticipated by Tang et al.

Specifically, the Examiner maintains the rejection over Tang et al because it is the Examiner's position that Applicants have not compared the peptide of Tang et al in the experiments in the specification, i.e., it is the Examiner's position that the polypeptide of Roose et al is not identical to that of Tang et al.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Tang et al discloses a protein having all HDs of human Lgs, and thus differs from the polypeptides of the present invention which do not contain both HD1 and HD2.

The peptides of the present invention have a surprising effect. They are negative regulators of the Wnt pathyway, and thus useful in cancer therapy. The prior art does not teach or suggest, or motivate a skilled person in the art to delete one or more of HD1 or HD2 from the hLgs protein of Tang et al.

The Examiner is requested to note that Roose et al, does not disclose Lgs peptides nor Lgs genes. That is, Roose et al discloses a tcf4-related protein which acts negatively on tcf-driven transcription. There is no structural homology or sequence identity between the tcf4-related protein and the claimed Lgs proteins.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Tang et al, and thus request withdrawal of the Examiner's rejection.

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,

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